



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

68/502
25 1/2 / Suppl
Response
RECEIVED *Watt*

Applicant: Lisbeth Illum

APR 29 1997

Serial No.: 08/359,937

Group Art Unit: 1502

GROUP 1500

Filed: December 20, 1994

Examiner: G. Kishore

Bel
4-30-97

For: SMALL PARTICLE COMPOSITIONS FOR
INTRANASAL DRUG DELIVERY

Assistant Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL RESPONSE

Sir:

In further response to the Office Action mailed from the U.S. Patent Office on September 27, 1996, Applicants enclose an analysis of the size of microspheres described in the cited art.

Claims 1-10 and 15-16 were rejected under the doctrine of obviousness-type double patenting as being obvious over claims 1-13 of U.S. Patent No. 5,204,108 to Illum.

Claims 11-14 and 17-28 were rejected under the judicially created doctrine of double patenting over U.S. Patent No. 5,204,108 to Illum.

Claims 1-6, 11-13 and 16 were rejected under 35 U.S.C. § 103 as being obvious over U.S. Patent No. 4,847,091 to Illum ("Illum"). Claims 1-28 were rejected under 35 U.S.C. § 103 as obvious over Illum in view of PCT WO 88/09163 by Illum (Illum PCT).

Claims 1-28 were rejected under 35 U.S.C. § 103 as obvious over Illum, L., *Nato ASI Symposium*, 125:205-210 (1986) ("Illum (1986)"). Claims 1-28 were rejected under 35 U.S.C. § 103 as being obvious over Illum in view of Hanson *et al.*, *Advanced Delivery Systems for Peptides and Proteins*, p. 233-242 (1988) ("Hanson"), or Salzman *et al.*, *New Eng. J. Med.*, 312:1078-1084 (1985) ("Salzman"), or vice versa. Claims 7-12, 14 and 23-26 were rejected under 35 U.S.C. § 103 as obvious over Illum (1986) in view of Hanson or Salzman or vice versa.

Enclosed is an analysis of the particle size of swelled and unswelled starch, DEAE-Sephadex and albumin microspheres, as disclosed in Illum (1986). These results demonstrate that starch microspheres swelled from approximately 23 microns in diameter to 43 to 46 microns; DEAE-Sephadex microspheres (represented to be less than 45 microns in diameter) swelled from approximately 44 microns to approximately 74 microns; DEAE-Sephadex microspheres (represented to be between 45 and 65 microns in diameter) swelled from approximately 60 microns to approximately 102 microns; and albumin microspheres swelled from (1) 196-214 microns to 270-283 microns; (2) 81-84 microns to 122-127 microns; (3) 142-145 microns to 200-209 microns; and (4) 18 microns to 27-30 microns.

These are all significantly larger, both prior to as well as after swelling, than the claimed microspheres, which must by definition be ten microns or smaller in diameter.

U.S.S.N. 08/359,937
Filed: December 20, 1994
SUPPLEMENTAL RESPONSE

Allowance of each of pending claims 1-28 is earnestly solicited.

Respectfully submitted,

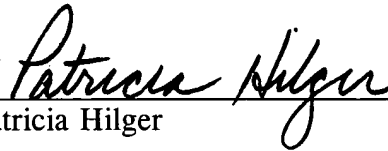


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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.



Patricia Hilger

Date: April 11, 1997



COMPARISON OF PARTICLE SIZE OF SWELLED AND UNSWELLED STARCH, DEAE-SEPHADEX AND ALBUMIN MICROSPHERES

WU LIN
21-03-97

Particles

1. Starch microspheres: Spherox 25/45 (dry size/swelled size), Pharmacia.
2. DEAE-Dextran microspheres: DEAE-sephadex A25, 40-125 μm (dry size), Pharmacia,
 - Pass 45 and 65 μm sieves to collect two fractions ($\leq 45 \mu\text{m}$ and 45 - 65 μm) for size analysis
3. Albumin microspheres: prepared using Helle Jorgensen's method (see *Int. J. Pharm.*, 39 (1987) 189-199 and unpublished booklet)
 - Since the size of the four paddle stirrer and beaker were not specified (beaker used in *Int. J. Pharm.* was 125ml whereas in the booklet was 250ml), two different four paddle stirrers and beakers were used to prepare albumin microspheres:

| Batch | Condition* |
|----------|---|
| 1-200397 | Small paddle, 250ml beaker, 50ml olive oil / 75ml petroleum ether |
| 2-200397 | Large paddle, 250ml beaker, 50ml olive oil / 75ml petroleum ether |
| 3-200397 | Small paddle, 150ml beaker, 50ml olive oil / 75ml petroleum ether |
| 4-200397 | Large paddle, 250ml beaker, 125ml olive oil |

*Other conditions such as stirring speed and time, crosslinker concentration and crosslinking time, albumin concentration, water/oil phase ratio, etc. are exactly same as those used by Helle Jorgensen.

Particle size measurement

- Small amounts of microspheres were dispersed in 5ml of ultrapure water (containing 0.05% Tween 80) and 5ml of propan-2-ol respectively. Samples were sonicated in a bath sonicator for 5 min before measurement.
- Analysis condition:
 - Malvern Mastersizer:
 - Focal length: 300 mm
 - Presentation: std
 - Medium: pure water for swelled particle size
propan-2-ol for unswelled particle size

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Result

| Particles | medium | D(4,3) | D(v,0.5) | Span |
|---|-------------|--------|----------|------|
| Starch | propan-2-ol | 23.00 | 22.38 | 0.63 |
| | pure water | 46.29 | 42.66 | 1.01 |
| DEAE-Sephadex ($\leq 45\mu\text{m}$) | propan-2-ol | 44.53 | 44.07 | 0.72 |
| | pure water | 74.42 | 73.31 | 0.90 |
| DEAE-Sephadex (45 - 65 μm) | propan-2-ol | 60.00 | 59.31 | 0.32 |
| | pure water | 101.77 | 102.07 | 0.51 |
| Albumin (1-200397) | propan-2-ol | 214.34 | 196.31 | 1.38 |
| | pure water | 283.63 | 269.97 | 1.06 |
| Albumin (2-200397) | propan-2-ol | 83.91 | 81.22 | 0.90 |
| | pure water | 127.14 | 121.97 | 0.84 |
| Albumin (3-200397) | propan-2-ol | 145.17 | 142.37 | 0.82 |
| | pure water | 209.61 | 200.27 | 0.70 |
| Albumin (4-200397) | propan-2-ol | 18.49 | 17.53 | 1.11 |
| | pure water | 30.06 | 27.02 | 1.56 |

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Kabi-Pharmacia

Physical description of starch microspheres.

Degradable starch microspheres consist of cross-linked hydrolyzed potato starch. The cross-links consist of glycerol ether moieties. In the cross-linking procedure non-crosslinking glycerol ether moieties are also introduced. The matrix is degraded to soluble polymers or oligomers by α -amylase. The time required for degradation depends on the degree of substitution.

The microspheres are manufactured by an emulsion polymerization process. By this process the mean diameter of the microspheres is regulated. The desired size distribution is achieved by wind-sieving of the microspheres in the dry form.

In aqueous media the microspheres swell to gel form. The degree of swelling depends on the degree of crosslinking.

STARCH MICROSPHERES 45/25

Starch microspheres 45/25 consist of starch cross-linked with epichlorohydrin. White, free-flowing beads. Swelled in sodium chloride solution 0.9% the microspheres have an average diameter of 45 μ m. They are completely dissolved by α -amylase solutions or body fluids containing amylase or by heating in aqueous acidic media. They are insoluble in all non-degrading solvents.

Amylase degradation, in vitro.

$T_{1/2}$ approx. 25 min

The half life, $T_{1/2}$ is defined as the time it takes for the microspheres to lose half of their mass by the action of α -amylase (240IU).

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KABI PHARMACIA**CERTIFICATE OF ANALYSIS****1991-12-17**Name **STARCH MICROSPHERES 45/25**Batch No. **10-1660-00**Batch No. **T 62423**

| Test | Result | Tolerance Limit | Test method |
|---|--------|-----------------|--|
| Amylase degradation T ₂ 240 IU, minutes | 26 | 10-40 | 02920 |
| Particle size distribution | | | |
| 20-70 µm, % w/v | 97 | Min 90 | 03634 |
| > 70 µm, % w/v | 3,1 | Max 5 | 03634 |
| < 20 µm, % w/v | 0,2 | Max 5 | 03634 |
| Loss on drying, % | 6,2 | Max 10 | 02678 |
| Residue on ignition, % | 0,1 | Max 10 | USP XXI Ph Eur 2nd ed JP X p 785 |
| Phosphorus, % | 0,05 | Max 0,1 | 03573 |
| Boron, ppm | 2 | Max 15 | 02206 |
| Alkydoting reactivity, ppm | <1 | Max 1 | 03558 |
| Toluene, ppm | <2 | Max 10 | 02962 |
| Ethanol, % | 3,3 | Max 7 | 03776 |
| Microbial total count, microorganisms/g | 2 | Max 102 | 02414 |

The identity is assured through strict adherence to established GMP rules throughout the manufacturing procedures.

Released for sale: 1993-09-06

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